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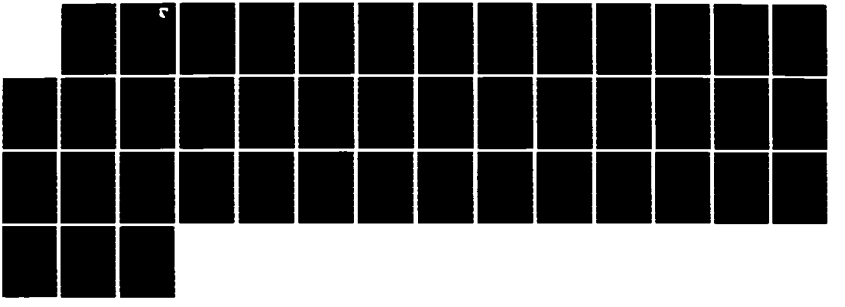

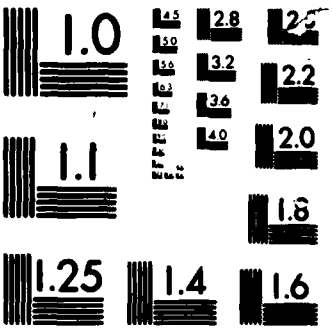

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AFAMRL-TR-85-036

DIAZEPAM AND ITS EFFECTS ON PSYCHOPHYSIOLOGICAL MEASURES OF PERFORMANCE (U)

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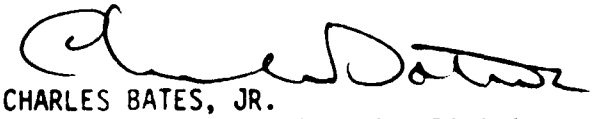
AFAMRL-TR-85-036

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

The voluntary informed consent of the subjects used in this research was obtained as required by Air Force Regulation 169-3.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER



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This study used a 5 mg oral dose of diazepam (valium) and placebo to test potential performance degradation under the influence of a minor tranquilizer. Dependent variables included a wide range of visual and auditory evoked response measures, as well as behavioral, memory, and physiological tasks that generated the measurement of 57 separate indices of human performance for each of 24 subjects during each of four measurement sessions. These dependent variables have been chosen as standardized tasks to be included in a neurophysiological test battery currently under development and testing by the Air Force Aerospace Medical Research Laboratory. This report describes the rationale for using these measures as indices of drug effects and outlines recent research using diazepam to induce performance decrements. Results of the experiment showed no generalized substantive effect at this dosage level on the performance variables studied. A multivariate analysis of variance for repeated measures, a contrast statistic, and a power analysis

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DIAZEPAM AND ITS EFFECTS ON PSYCHOPHYSIOLOGICAL MEASURES OF PERFORMANCE (U)

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were performed to substantiate this finding. The averaging and analysis capabilities of the test battery were successfully tested, and its use in further tests of drug/chemical nerve agent testing is planned and discussed. (Keywords:

PREFACE

The purpose of this study was to test the effects of a 5 milligram oral dose of diazepam (valium) on performance as measured by the Neurological Workload Test Battery (NWTB). The research effort was performed in support of AFSC Project 7184, Man-Machine Integration Technology, by the Air Force Aerospace Medical Research Laboratory (AFAMRL), Human Engineering Division, Wright-Patterson Air Force Base, Ohio 45433.

The study was proposed by the first author as a research project in partial fulfillment of the requirements for a doctoral degree while assigned to Bowling Green State University, Bowling Green, Ohio, under Air Force Institute of Technology (AFIT) sponsorship.

The authors gratefully acknowledge the contributions of Mr. David Ratino and MSgt Gregory Bathgate (AFAMRL/BBS) who designed and built the EMG equipment; Ms. Karen Peio, Ms. Barbara McFawn, Ms. Kathy McCloskey, Ms. Heather Dipple, Ms. Iris Davis, Ms. Jennifer Zingg (SRL), and Major Loretta L. Floyd (AFAMRL/HEG) who assisted in subject preparation, screening, data collection, analysis, and hardware/software development and maintenance; and Drs. Charles Hatsell (AFAMRL/CV), David Toth (AFAMRL/BBD), and George Potor (AFAMRL/BBS) who provided medical screening, postexposure assessment, and backup.

TABLE OF CONTENTS

LIST OF TABLES

Section 1
INTRODUCTION

Since much research has demonstrated the potential applicability of the visual and auditory evoked response (VER and AER) in assessing physiological, behavioral, and cognitive functioning (Beck, 1975; Chiappa and Ropper, 1982; Davies and Parasuramen, 1977; Donchin, 1968; Donchin and Cohen, 1967, 1969; Donchin and Sutton, 1970; Kutas, McCarthy, and Donchin, 1977; Regan, 1975, 1977a, 1977b; Shaefer, 1977), several laboratories have committed themselves to both basic and applied research using the evoked response as a potential performance measure. This type of research would be enhanced if it were possible to reduce the expense and the number of the various pieces of equipment currently required for its pursuit. Of even greater benefit would be the development and validation of a standard set of metrics to assess the VER and AER in as pure a form as possible. The purpose of the current project was to use the most current advances in equipment technology coupled with evoked response methodology to test the feasibility of combining the capabilities of stimulus generation, averaging and storage of the resulting response, and measurement of the final waveform parameters of interest in a single instrumentation package.

Both the transient and steady state evoked responses have found considerable utility in research involving neuropsychological and clinical assessment. Several separate lines of research over the past decade have focused on discrete aspects of the human evoked response in an effort to demonstrate its validity and reliability as a diagnostic tool. For example, the visual evoked response has been studied extensively in terms of its ability to assess visual acuity. Harter and White (1970) were among the first to note that there were systematic changes in the transient visual evoked response to a patterned stimulus with progressive defocusing. These authors, using a checkerboard pattern flashed at the rate of once per second (1 Hz), found that the subjects' averaged electroencephalographic (EEG) response contained peaks that were maximal when the image was in focus. These authors suggested that the spherical correction for an unknown eye could be determined by systematically inserting corrective lenses until an optimal evoked response was obtained. Since further study demonstrated this measure to be

a sensitive and objective index of acuity (Marg, Freeman, Peltzman, and Goldstein, 1976), correlating with more tediously determined psychophysical thresholds, its impact in clinical diagnostics has been considerable.

Increased applicability of this technique was obtained by Regan (1977a) who flashed the checkerboard at a faster rate (7 to 15 Hz) and obtained a sine wave (steady state) output from the brain whose averaged amplitude was an equally good index of visual acuity. The amount of time required to obtain the response in this manner was, thus, drastically reduced. Further refinements of the technique (Regan, 1977a) resulted in the ability to generate this measure without intruding with an ongoing visual task. It is this nonobtrusiveness, along with its precision, that makes the evoked response an attractive technique for human engineering, medical, and educational applications since data can be collected while not interfering with the subjects' primary performance.

Use of the evoked response (both transient and steady state) is by no means limited to visual acuity. Both the absolute latency and the difference in latency between the two eyes tested monocularly are sensitive indicators of visual pathway functioning. A recent review by Chiappa and Ropper (1982) discusses the use of these measures as indicators of such diseases as optic neuritis, multiple sclerosis, glaucoma, Parkinson's disease, amblyopia, and lesions and tumor compression of the anterior visual pathways.

An evoked response can also be generated to auditory stimulation. Several studies (Davis, 1976; Hecox and Galambos, 1974; Jewett and Williston, 1971) have described a click evoked response recorded from the human scalp in the first 10 msec after stimulation. The normal response can be divided into distinct peaks that originate in specific midbrain and peripheral structures along the auditory pathway. Further, this response is independent of the cortical state of the subject. Thus, testing can be accomplished with the subject awake, asleep, sedated, or while he is attending to another task--enhancing its usefulness as a nonobtrusive measure of auditory function.

The transient evoked response has also proven to be an extremely durable measure of cognitive relevance. After it was recognized that the evoked

responses to relevant stimuli were larger than those to nonrelevent stimuli (Chapman, 1965), several investigations set about establishing the parameters of the response which measured such relevance (Beck, 1975; Donchin et al., 1967, 1969, 1970). It became clear that the major characteristic of the evoked response sensitive to cognitive function is the large positive peak which occurs between 200 and 500 msec poststimulus. This peak is absent if decision or attention is not required from the subject and, when it occurs, seems to be capable of indexing a wide variety of stimulus meaning and relevance. Beck (1975) reviewed the literature dealing with this positive component (called P3 or P300) and concluded that it is enhanced when and only when cognitive information is being actively processed. Further study of the amplitude and latency measures of the P300 and its associated peaks (both pre and post) have identified characteristic changes that occur in its morphology due to memory load, fatigue, reaction time, and information processing time (Chapman, 1973; Donchin and Lindsley, 1966; Gomer, Spicuzza and O'Donnell, 1976; Squires, Wickens, Squires, and Donchin, 1976).

The discovery of the evoked potential and the research described above has done much in terms of providing an objectively measurable indicator of several aspects of human performance and condition. However, the range of equipment required to carry out this type of research is staggering both in numbers and in expense. The computers, stimulus equipment, calibrators, filters, amplifiers, recording devices, and analysis devices typically fill an entire laboratory and can be configured to study only one type or aspect of the evoked response at a time. To change, for example, from studying the evoked response to patterned stimuli to an experiment designed to analyze the P300 response to a memory task requires disconnecting equipment, introducing new stimulus devices, recalibrating filters and amplifiers, changing software, and connecting a completely different analysis device. The study of this important human response would be enhanced if it was possible to construct a single device which incorporated stimulus generation, storage, and analysis capabilities. Interlaboratory standardization of measurement would also be an important consequence of such a device. Access to the prototype of such a device has been provided by the Air Force for the purposes of this study. The individual tests that were chosen for this study were

incorporated into the software of the device (hereafter referred to as the test battery) and, thus, provided all the advantages of several separate pieces of stimulus and analysis equipment currently found in clinical and laboratory settings.

Once its reliability and validity were established by field testing, the battery could be hard wired and, by means of extensive interpretation guides, administered, analyzed, and interpreted by technicians, hospital staff, and trained laboratory personnel without extensive professional assistance. The microminiaturization of such a battery would allow its incorporation into human operated machine design to detect operator fatigue, perceptual distortion, and performance degradation. A simple feedback loop could be incorporated in the equipment to provide warning once amplitudes and latencies exceeded a preset limit. The combination of cognitive, perceptual, and behavioral tasks would enable the battery to be used in educational/assessment facilities. Software incorporation of other measures specific to learning ability or specific capacities desired in a work environment would allow the battery to be used in learning disability assessment and in job selection where potential workload is high. The military has obvious interest in such a device as a means to imbed performance assessment capabilities into human operated weapons systems. Interest has also been expressed by NASA which could incorporate such a device in space environments where optimum human performance is essential in man/machine interaction. The sensitivity of the proposed measures to neurological damage, demyelination, and visual and auditory pathway lesions would have implications in terms of the clinical assessment of neurological integrity and diagnosis. In experimental/human engineering settings, it is possible to conceive of the battery being used as a standardized measure of fatigue, psychological distress, and attention in both basic and applied settings.

In line with these proposed uses, the battery must be able to measure visual, auditory, behavioral, cognitive, and physiological performance either singly or simultaneously in a variety of settings. The problem that arises at this point is how to calibrate the battery, i.e., to develop a standard against which to gauge the potential performance decrement in question. Most logically, use of an agent with known decremental effects on the

measures would be an appropriate first step. Measurement of a known drug effect would serve the purposes of testing the battery's sensitivity to a fixed dosage level and calibrating the battery to use the measured effect as a standard against which to later gauge the effects of a variety of chemical agents or conditions that produce similar decrements.

Several evoked response measures have been shown to exhibit considerable psychophysiological sensitivity to the benzodoazepines. Chlordiazepoxide, nitrazepam, oxazepam, and diazepam have generally been found to impair psychomotor skills, depress critical flicker fusion and auditory flutter fusion thresholds, increase the latency and decrease the amplitude of both somatosensory and visual evoked potentials, decrease subjective mood levels and attentiveness (Kleinknecht and Donaldson, 1975; Shagass, 1974; Shagass and Straumanis, 1978; Sherwin, 1971). The drug that produces the most consistent effects on these measures is diazepam (valium). The relative absence of adverse side effects with clinical doses (.05 to 10 mg iv, 5 to 20 mg po), less drowsiness, overdose potential, and tolerance effects made diazepam an ideal drug for this study. Learning and memory tasks have also been used to study the decremental effects of diazepam exposure and have resulted in the conclusion that diazepam impairs the retention of new information rather than the retrieval of previously learned material (Clarke, Eccersely, Frisby, and Thornton, 1970; Haffner et al., 1973; Liljequist, Linnoila, and Mattila, 1978). Finally, both workload level and diazepam induce similar decrements in the amplitude and increases in the latency of various components on the evoked response. These, combined with an increased error rate and longer reaction times, have been found to correspond to decrements in attention, psychomotor skills, perception, vigilance, and cognitive performance capabilities (Donchin, 1977; Rizzuto and O'Donnell, 1981; Seppala, Pavla, Matilla, Kortilla, and Shrotriya, 1980; Wickens, Israel, and Donchin, 1977; Wilson and O'Donnell, 1980). Accordingly, a wide range of evoked response and clinical measures were chosen for this study that would be sensitive to diazepam induced performance decrements. The aim of the study was to use this battery of tests to (1) ascertain their measurement of overall performance effects during human exposure to a single oral dose of diazepam and a placebo, (2) gauge which of the subtests, if any, are differentially sensitive to diazepam, (3) test the averaging and analysis capabilities of

the battery, and (4) upon finding these answers, further refine the battery for its employment in further research and validation.

Section 2
METHOD

SUBJECTS

Air Force active duty male volunteers were solicited through base-wide advertisement in a weekly bulletin at Wright-Patterson Air Force Base, Ohio. Potential subjects were administered the Cornell Medical Index (Weider, Wolff, Brodman, Mittelmann, and Wechsler, 1949) to screen for psychosomatic and neuropsychiatric disturbance. A stringent cutoff level was established allowing rejection of any subject scoring seven out of 101 possible affirmative answers. This cutoff allowed rejection of approximately 90 percent of all testees with indications of a neuropsychiatric or psychosomatic disorder. The potential subjects were next interviewed by the principal investigator who ascertained family and individual psychiatric and medical history, past and current medication use, allergies to any drugs, previous diazepam experience, seizure history, visual and auditory difficulties, alcohol use, glaucoma history, depression, suicidal tendencies, and a subjective evaluation of the individual's emotional stability. Finally, the volunteers were given a brief medical examination by an Air Force physician who measured blood pressure and resting heart rate, administered the Rhomberg and Finger-Nose Task to assess organic brain dysfunction, and made a final evaluation regarding any medical or psychiatric history that was in question.

In this manner, 24 male subjects were selected for the experiment. Each was given both an oral and a written explanation of the study, provided the opportunity to ask questions, and asked to sign a consent form. Subjects were told that the study was to evaluate the effects of various substances on several performance measures, and that one of the substances of interest that they may have heard about previously was valium. All 24 agreed to participate.

PROCEDURE

Prior to their actual day of service, subjects were introduced to the laboratory, seated inside the sound and light proof test chamber, and given exposure to each of the tasks on which they were to be measured. The tasks were presented in the same order as they were to be presented during the experiment and consisted of the steady state evoked response to an unpatterned stimulus, a short term memory task designed by Sternberg (1969), a grip strength and grip duration task, an auditory discrimination task, the steady state evoked response to a patterned checkerboard stimulus, the transient evoked response to a strobe light, and a critical flicker fusion threshold measurement. Each of these is described in more detail below. This gave each subject the opportunity to familiarize himself with the mode of stimulus presentation and to practice those tasks requiring subject response. Subjects were then scheduled for two service days separated by a 48-hour intersession interval (to allow the ingested diazepam to pass from the system between actual measurement days). Subjects were cautioned not to ingest any alcohol or medications for 12 hours pre and post each measurement session. They were also advised to get a normal night's sleep prior to the day of their participation and to eat a light breakfast beforehand. Each was asked to verify these conditions on the days of service.

The study itself employed a double blind, two session (diazepam and placebo) repeated measures design with each subject acting as his own control. Thus, on his first day of participation, each subject was first tested on each of the measures to establish baseline levels--hereafter referred to as "Baseline 1." After completion, the principal investigator administered and observed ingestion of one of two possible unmarked capsules taken from separately numbered bottles. One bottle contained 5 mg capsules of diazepam, and the other an identical capsule containing the placebo. The balanced design resulted in 12 randomly assigned subjects receiving a capsule from bottle number one on their first day of service and 12 subjects receiving a capsule from bottle number two on their first day. Since the peak effect of the diazepam was expected approximately 1 hour postingestion (Physician's Desk Reference, 1979) and subject measurement time was approximately 30 minutes, the retests were not begun until 45 minutes postingestion. This

resulted in peak drug effect occurring during the middle of each measurement session. The retests were administered in the same order as the baseline sequence in order to obtain approximately equal test/retest time periods. At the completion of the retest session, subjects were again checked by the physician, if necessary, to assess any symptoms that would preclude their returning to work or transporting themselves to their duty station. When cleared, they were given a form with the principal investigator's telephone number and told to contact him, should any symptoms develop. The same instructions were given in terms of alcohol, drugs, sleep, and breakfast before their next measurement session, and they were allowed to leave. In this manner, three subjects were run each morning between 8:00 a.m. and 12:00 noon to ensure that any possible drug effects would be gone by the end of the duty day, and to control for circadian effects. Two mornings later, the subjects arrived in the same order and the same baseline/ingestion/ retest procedure was followed. The only difference was that each subject was administered the capsule he had not received on his first day of service.

Section 3
EQUIPMENT/TESTING SEQUENCE

During measurement sessions, electroencephalograms were recorded on magnetic tape from both the occipital (OZ) and parietal (PZ) lobes via Beckman silver/silver chloride electrodes attached to the scalp with adhesive collars according to the international 10-20 electrode placement system (Jasper, 1958). Electrodes were also placed on each mastoid process; one was used as a reference, the other as a ground. Resistance between the electrodes was less than 5 Kohms. Electro-oculograms were recorded in the same manner from an electrode placed above the right eyebrow, and electromyograms were recorded from a triplet of surface electrodes placed over the flexor digitalis muscle of the dominant forearm. All electrical data from the skull were amplified and filtered through standard Grass P511 AC amplifiers with an effective bandpass of 0.1 to 300 Hz before recording. Electromyographic data were amplified by a separate electromyographic amplifier before recording. All subjects were visible to the experimenters by means of a TV camera trained on the subject's face and connected to an external monitor outside the subject booth. Leads from the skull were attached to a patch box which fed subjects' data to all measurement equipment outside the subject booth. All stimuli were visible through a glass window in the wall of the subject booth approximately 80 cm from where the subjects were seated. The prototype battery, Neuropsychological Workload Test Battery (NWTB), consisted of an LSI 11/23 microprocessor utilizing 16 channels of amplified physiological and psychophysiological data. The NWTB was used to control stimulus presentation and ultimately averaged and analyzed most of the subjects' data. A Honeywell Model 600B FM tape recorder was used to store the physiological data and event markers. The sequence of tests during each of the four measurement sessions (Baseline 1, Day 1 Postingestion, Baseline 2, Day 2 Postingestion) and the apparatus specific to the individual tasks is given in the following paragraphs.

STEADY STATE EVOKED RESPONSE TO UNPATTERNED STIMULI

The steady state evoked response was elicited by two horizontal flickering fluorescent tubes, 23.5 cm long and 12.1 cm apart, viewed through the window

of the subject booth at a distance of 81.3 cm. The subject was told to fixate on a black dot centered between the tubes on a white background and not to blink during the test. The tubes were sinusoidally modulated at three separate frequency classes (low, medium, high), each consisting of the sum of four separate frequencies within the class (8, 9, 10, and 12 Hz for low; 16, 18, 20, and 22 Hz for medium; 45, 48, 51, and 54 Hz for high). The sum of each sine wave set within a class was generated by a PDP 11/60 computer and stored on an Ampex SP300 analog tape. Signals from the SP300 were used as input to drive a Scientific Prototype Tachistoscope, Model G.B., modified so that the tube intensity could be modulated from an external oscillator. The space averaged luminance of the stimulus tubes ranged from 40 to 57 footlamberts (fL), with a modulation depth of 20 percent. The measurement of stimulus and EEG data, averaged over 20 1-second epochs for each stimulus class, was carried out by a Nicolet Model 660A spectrum analyzer and stored on disc for later analysis.

STERNBERG SHORT TERM MEMORY TASK

The subject was then given a brief rest, the fluorescent tubes were turned down to minimum luminance, and the white background was removed to reveal the TV screen used for the memory scanning task. The subject was then told that he would be presented with a single, two digit number in the screen which he was to memorize. When he indicated that he was ready by means of a nod of the head, a microcomputer program would begin presenting random, two digit numbers (negative set) some of which would be the memorized number (positive set). He was then told to decide as quickly and as accurately as possible to which set the number belonged, and to indicate his choice on a two-button, handheld response box. The subject was given as much time as desired for memorization and was cautioned not to blink during number presentation. After the presentation of 40 numbers, the program was recycled to present a three-number and a five-number memory set following the same procedure. Each number was approximately 20 mm wide and 12 mm high with an average luminance of 600 fL. Each number was on the screen for 100 msec and the interstimulus interval was randomly generated to between 1.5 and 2 seconds. The proportion of positive to negative set numbers was fixed at 50:50 resulting in 20 positive and 20 negative trials. Two-digit numbers were

used to avoid the repetition of any number during the practice or the four experimental runs. During the presentation of each memory set, the microprocessor stored the response to each letter in terms of correct/incorrect and reaction time from the onset of the letter to the button press. These data were also sent to disc for later analysis. In addition, a trigger pulse was generated to the onset of each letter, both positive and negative, and recorded along with the raw, continuous EEG and EOG to serve as a marker that would allow for future analysis of the electroencephalographic and eyeblink response to each decision point.

GRIP STRENGTH AND ELECTROMYOGRAMS

At the completion of the Sternberg memory task, the lights in the subject booth were turned on and the principal investigator entered the booth. The leads from the three arm electrodes were connected to one channel of a battery powered, two channel electromyographic amplifier which utilized an Analog Devices 521 instrumentation amplifier with a frequency response of 2 to 5000 Hz. Electromyographic response was verified visually on a standard oscilloscope by having the subject make a fist and squeeze. The subject was then handed an SRL handheld dynamometer with strain gauge. The dynamometer was connected to the second channel of the amplifier and to a 500 microamp DC meter which served as a dynamic tension indicator. The subject was then told that on the count of three, he should squeeze the dynamometer as hard as he could in one maximum concerted effort and then to let go immediately. The three count was necessary to insure that the experimenter was watching the tension meter in order to record the point of maximum displacement. As a backup, an assistant also entered the booth and watched the meter to verify the meter displacement. The number was recorded on the subject data sheet. After a brief rest, the subject was again told to take the dynamometer in hand and, on the three count, to squeeze as hard as he could but to maintain the squeeze at maximum level until told to let go. During this second squeeze, the EMG was recorded on analog tape for later frequency analysis.

AUDITORY ODDBALL TASK

The subject was next handed a pair of lightweight earphones and told that he would be presented with a series of tones--some low (1200 Hz) and some high (1400 Hz). He was also told that the low tones would occur less frequently (hence, the term "oddball") and that the task would be to count the number of low tones. After the subject was seated back comfortably with eyes closed (to control for eye movement and blinks) and earphones in place, the task was begun. The microcomputer presented 100 tones at two-second intervals. The length of each tone was 100 msec and the proportion of high to low tones was randomly varied resulting in 20 to 25 percent low. In addition, the program generated a trigger pulse 150 ms prior to the onset of each tone which was recorded along with the EEG to serve as a marker for analysis of the brain's response to each tone presentation and decision. At the conclusion of task, the principal investigator again entered the booth and recorded the number of low tones the subject reported counting beside the number of low tones the computer indicated it had generated.

STEADY STATE EVOKED RESPONSE TO PATTERNED STIMULI

Next, the low frequency steady state evoked response was collected. The subject's attention was again drawn to the television screen. A Checkerboard Generator was used to produce a full screen black and white checkerboard pattern with checks 0.7 cm square. The subject was told to fixate on the center of the screen while the pattern was set to flicker at 7.5 Hz for approximately 1 minute. Measurement did not begin until 10 seconds after the stimulus had begun to flicker in order to allow the brain time to settle into a steady state response condition. A Nicolet CA 1000 Clinical Signal Averager was used to analyze the occipital EEG. The evoked potential consisted of the average to 64 samples--each triggered on the first stimulus flicker after completion of data collection for the previous sample. Sweep epoch time was 500 msec. At the completion of the 64th sample, the average was stored in one of four channels of internal memory in the CA 1000. The subject was given a brief rest, and the checkerboard was set to flicker at 10 Hz for another 64 samples. When that average was stored, the flicker rate was set at 15 Hz for the third and final 64 sample average. As backup

to the Nicolet, raw EEG was recorded to each frequency presentation. Unlike any of the tasks preceding it, the averaged response was not stored for future analysis. This required the principal investigator to set the CA 1000 to plot the averaged waveform for each stimulus frequency and to manipulate a cursor in order to label each peak of interest with its amplitude and latency in order to free the memory of the CA 1000 for the next subject's data. This was done, however, after each subject's completed run.

TRANSIENT VISUAL EVOKED RESPONSE

The transient visual evoked response was next generated using a Grass Model PS-22 Photostimulator. The face of the strobe light was 13.3 cm in diameter, with an average intensity of 4.8 x 103 fL at the lamp. The strobe was set to flicker at 1 Hz and the subject was told to fixate on the center of the lamp, blinking only during the interflash interval, until told to stop approximately 1.5 minutes later. During stimulation, 500 msec samples of EEG were triggered to the onset of each of 100 2-microsecond flashes. The samples were averaged by the CA 1000 and the averaged waveform was stored in its fourth memory channel for amplitude and latency measurement between subject sessions.

CRITICAL FLICKER FUSION THRESHOLD

The final task determined the critical flicker fusion threshold frequency. The subject was told to close his eyes as the experimenter increased the strobe flicker rate to 10 Hz. From there, the experimenter increased the flicker rate in 1 Hz increments per second. The subject was told to raise his hand when the light seemed to stop flickering and became a steady, fused light. The frequency at which the lamp was flickering when the subject raised his hand was then recorded. The lamp was then increased to its maximum flicker rate. The experimenter then decreased the flicker rate by the same increments and the subject was told to raise his hand at the first perception of flicker. That frequency was also recorded and the average of the two was calculated and taken as the critical flicker fusion frequency.

Section 4
RESULTS

Subjects were administered the series of tasks described above and generated the measurement of 57 separate dependent variables per subject during each of the four measurement sessions. Raw data were tabulated and subjected to a modified multivariate analysis of variance for repeated measures using BMDP4V. In addition to an overall significance level for differences in the dependent variable over the four measurement periods, the analysis yielded a contrast statistic, Hotelling's T^2, for each of the comparisons of interest (Baseline Day 1 versus Baseline Day 2; Baseline Day 1 versus Placebo; Baseline Day 2 versus Placebo; and Baselines and Placebo versus Valium). In order to correct the program's reported degrees of freedom, an SAS program was written using matrix manipulations that converted these T^2s to exact F statistics and calculated their associated probabilities. Although much of the test equipment performed flawlessly, both hardware and software malfunctions caused the loss of differing amounts of some of the subjects' data on individual dependent variables. In both instances, this process allowed for adjustments in the varying degrees of freedom not accurately taken into account by the BMDP program. Using an alpha level of 0.10 in an attempt to decrease type II error (as will be used throughout the analyses), the resulting matrix of probability values indicated no significant differences between the baseline measurements or between the placebo and each day's baseline. The degrees of freedom ranged from 3 and 14 to 3 and 21, and the general range of the P values was between .70 and .99. Thus, it made sense to average the baselines with the placebo measurement and to make the final comparison of the average of these three with the results of the valium ingestion session.

VISUAL TESTS

The individual means for the components of the visual tests are presented in Table 1 along with their associated P values.

TABLE 1. SESSION MEANS FOR VISUAL TESTS

Measure	Frequency/ Component	Baseline 1	Placebo	Baseline 2	Valium	P
Checkerboard	7.5 Hz	30.57	31.33	27.43	23.65	.06*
Amplitude	10 Hz	26.37	31.42	25.89	23.53	.24
(arbitrary units)	15 Hz	18.90	10.08	17.32	15.38	.04*
Checkerboard	7.5 Hz	.1162	.1152	.1184	.1199	.53
Latency	10 Hz	.0632	.0619	.0572	.0675	.03*
(sec)	15 Hz	.0498	.0501	.0503	.0516	.90
Strobe	(N1, P1)	27.63	27.66	28.74	28.09	1.00
Amplitude	(P1, N2)	28.19	30.22	30.61	31.61	.66
(arbitrary units)	(N2, P2)	36.67	37.49	37.12	35.39	.93
	(P2, N3)	31.89	33.21	34.55	30.77	.64
Strobe	(N1)	.0764	.0757	.0756	.0743	.94
Latency	(P1)	.1108	.1122	.1087	.1092	.98
Components	(N2)	.1499	.1482	.1472	.1517	.70
(N1-N3)	(P2)	.2042	.2045	.2039	.2104	.35
(sec)	(N3)	.3050	.3044	.3051	.3660	.45
SS Mean	Low	.1617	.1637	.1658	.1247	.10*
Coherence	Medium	.2156	.2352	.2459	.1651	.02*
	High	.0963	.0885	.0970	.0950	.99
SS Mean	Low	.0734	.0821	.0666	.0686	.80
Amplitude	Medium	.0410	.0398	.0336	.0379	.99
(arbitrary units)	High	.0213	.0182	.0179	.0181	.99
SS Trans	Low	229.30	217.70	219.20	169.10	.45
Speed	Medium	121.70	143.10	150.50	138.80	
(msec)	High	96.50	129.10	122.30	136.50	
CFF	Hz	21.73	22.44	22.25	22.38	.96

*Significance of $p \leq .10$.

The low frequency steady state evoked response to patterned (checkerboard) stimuli yielded measures of both amplitude in arbitrary units, and latency in either milliseconds (msec) or seconds (sec). Representative tracings for a single subject are presented in Figure 1.

As can be seen, the checkerboard reversing at a frequency of 7.5 Hz produced a characteristic sine wave output (1A) usually containing 3 1/2 positive going peaks--roughly half of the stimulating frequency. Similarly, 10 Hz

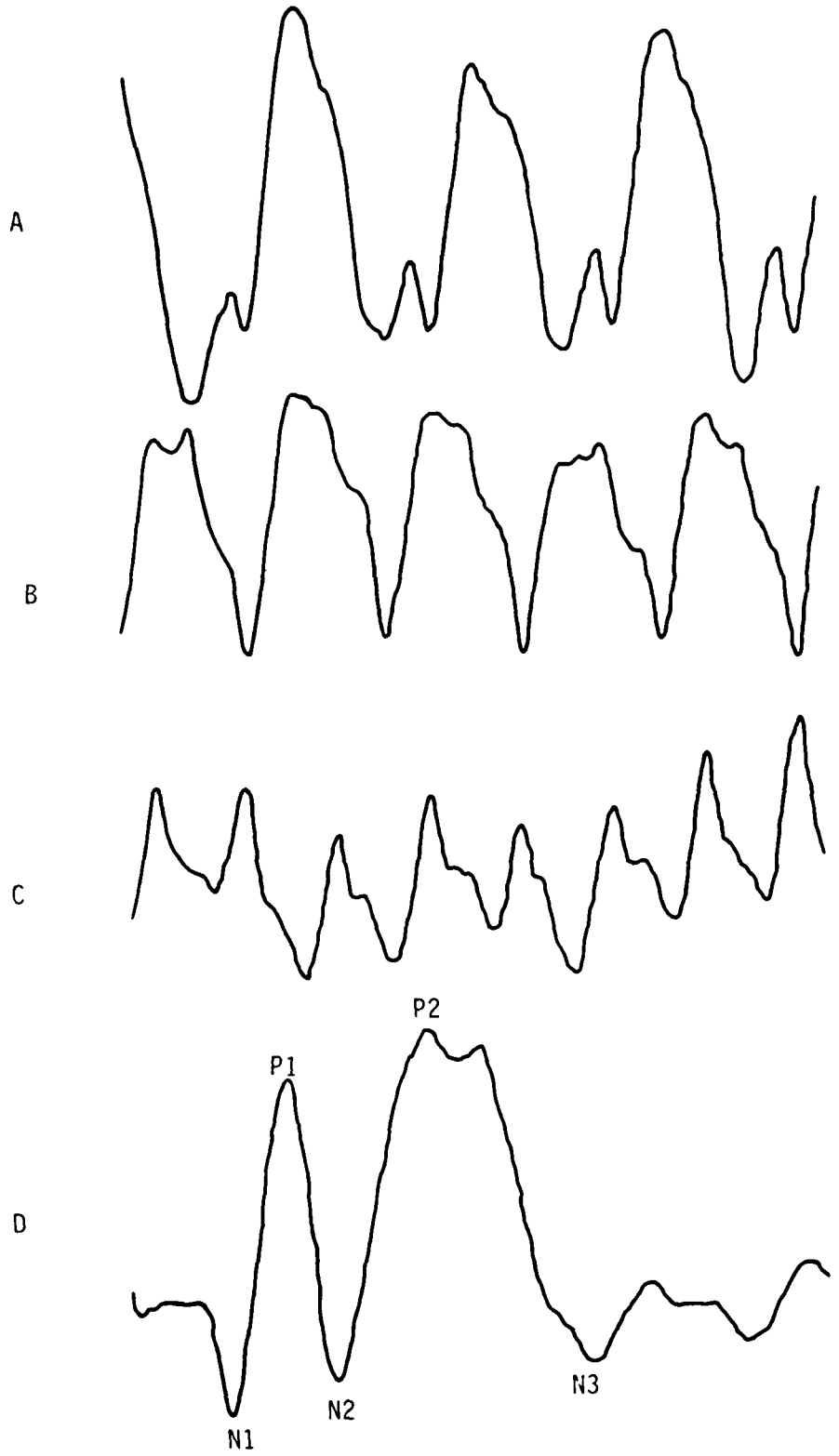

Figure 1. Tracings for a Typical Subject in Response to Steady State Checkerboard Stimulation (A = 7.5 Hz, B = 10 Hz, C = 15 Hz) and strobe light (D)

and 15 Hz stimulation (1B and 1C) produced five and eight peaks, respectively. Amplitude measurements were taken from each positive peak and an average amplitude was calculated for each stimulating frequency. The amplitudes of both the 7.5 and 15 Hz responses were significantly decreased ($P = .06$ and $.04$) by valium ingestion while the amplitude decrease of the 10 Hz response failed to attain significance. From these same tracings, the latency of the first complete positive peak was measured and, although all latency measures indicated an increase, only the latency increase of the 10 Hz response attained significance ($P = .03$).

In a similar fashion, amplitude measurements of the transient evoked response to the stroboscopic stimulation (1D) were taken. However, since with the strobe the precise onset of the stimulus is known and the characteristic output trace is not a sine wave, each component peak is measured individually from its associated trough. Thus, the distance of the two major positive peaks (P1 and P2) from the three negative troughs (N1, N2, and N3) comprise the four amplitude measurements for the transient response. The latency from the onset of stimulation to each of these five individual peaks was also measured. Although the early peaks, N1-P1 and P1-N2, showed an increase in amplitude and a decrease in latency, and the later peaks showed an opposite effect, none of the results achieved significance.

The mean coherence function of the steady state evoked response to unpatterned stimulation reflects a gross correlation between the spectral analysis of the four input frequencies in each stimulus category (low, medium, and high) and the spectral analysis of each peak of the resulting brain response. Significant valium induced decreases in the coherence function between input and output were achieved for both the low and medium frequency classes ($P = .10$ and $.02$, respectively) but not for the high frequency class. The same battery software analysis of these data also produced a measure of the amplitude of each response peak. An average amplitude to each response class was calculated in the same manner as for the checkerboard amplitudes and was compared across the four measurement conditions.

Although the amplitude of the response to each stimulus class did decrease after the valium ingestion, the changes failed to reach signficance.

The apparent latency of the visual system's transmission speed is obtainable from the final set of measurements of the steady state response to unpatterned stimuli. A Fast Fourier Transformation algorithm was used to calculate the phase lag between the sine wave used as input and the sine wave obtained from the brain as output. The slope of this phase lag was determined by linear regression and the result was divided by a constant 360 degrees. The final result is the apparent latency of the visual system, i.e., the amount of delay between input and output in the averaged EEG. A caveat is in order here. If the coherence value of the individual peaks is less than or equal to 0.05, it indicates that the output cannot be meaningfully distinguished from the surrounding EEG noise and, therefore, cannot be interpreted. As a consequence, if more than two of the four output peaks are so classified by this criterion, a slope cannot be determined and the subject's data are dropped from the appropriate frequency class analysis. As a result of this procedure, eight, four, and 16 subjects' data were eliminated from the low, medium, and high frequency class transmission speed analyses, respectively. Since the medium and high frequency classes were the only subtests to have their respective degrees of freedom reduced by these amounts, exact F values and their associated probabilities could not be calculated. The apparent latency change for the low frequency class was obtainable but failed to reach significance.

The final visual test to be analyzed was the critical flicker fusion frequency. The average of the ascending and descending fusion frequencies was tabulated and showed no significant changes across measurement sessions.

STERNBERG MEMORY TASK

The means and associated probabilities for the Sternberg short term memory task are presented in Table 2.

TABLE 2. SESSION MEANS FOR STERNBERG MEMORY SET TASKS

Measure	M Set	Baseline 1	Placebo	Baseline 2	Valium	P
Percent Correct	Negative M Set 1	90.88	91.18	93.63	91.47	.99
	Positive M Set 1	96.18	97.06	95.88	95.29	.82
	Negative M Set 3	91.39	93.06	93.36	91.67	.95
	Positive M Set 3	91.94	93.06	93.89	90.83	.58
	Negative M Set 5	91.94	93.06	92.50	90.28	.60
	Positive M Set 5	90.83	89.17	90.83	85.83	.29
Mean Reaction Time (msec)	Negative M Set 1	523.90	540.40	532.40	552.90	.71
	Positive M Set 1	520.70	515.00	527.40	533.50	.92
	Negative M Set 3	658.10	638.30	645.60	647.40	1.00
	Positive M Set 3	653.10	625.40	635.20	624.60	.64
	Negative M Set 5	723.00	737.90	704.90	771.80	.14
	Positive M Set 5	665.80	710.70	669.40	697.30	.89
Slope	Negative Set	49.01	49.31	43.03	55.54	.75
	Positive Set	36.45	44.74	36.98	42.48	.99
P300 Amplitude (arbitrary units)	Positive M Set 1	146.10	150.80	142.10	152.40	.89
	Positive M Set 3	127.80	127.90	135.70	131.60	.99
	Positive M Set 5	125.10	121.10	124.60	125.10	.99
	Negative M Set 1	116.40	108.80	117.80	115.00	.99
	Negative M Set 3	99.72	114.20	116.30	108.30	.99
	Negative M Set 5	88.56	100.30	101.70	98.33	.99
P300 Latency (msec)	Positive M Set 1	361.70	356.90	359.70	365.80	.98
	Positive M Set 3	426.10	411.10	431.90	407.50	.83
	Positive M Set 5	465.30	436.40	448.10	390.30	.08*
	Negative M Set 1	398.60	407.20	371.70	369.70	.61
	Negative M Set 3	444.40	446.70	442.80	411.70	.59
	Negative M Set 5	414.40	445.80	424.40	384.40	.15

*Significance of $p \leq .10$.

The analysis of this task was divided into five subanalyses. The response time to each of the 40 stimulus numbers for each of the three memory sets was tagged with either a (+) for correct or a (-) for incorrect. This allowed the calculation of the percent of correct responses as well as a mean reaction time to both the positive (memorized) and negative (nonmemorized) number sets. As mentioned earlier, the proportion of positive to negative numbers was fixed at 50:50 in order to keep the amount of memorized information presented to the subject for decision at a constant level. A software error in the stimulus presentation algorithm resulted in a variable rather than an equal proportion of stimulus presentations to the first six

subjects. Therefore, these six subjects' data were removed from the Sternberg analysis. As can be seen in Table 2, neither the decrease in the percent of correct responses to the individual memory sets nor the general increase in the mean reaction time measured from the onset of the stimulus numbers was significantly affected by valium. Also, the increased slope of the mean reaction times to both positive and negative sets considered collectively, which reflects increased scanning and processing time, did not attain significance.

As described in the previous section, the raw EEG during the Sternberg task was also recorded for off-line analysis by the battery. Individual EEGs to each stimulus letter were analyzed for an epoch of 150 msec pre to 845 msec post stimulus and displayed along with the accompanying eyeblink (EOG) trace. This allowed individual trials to be viewed and either kept or discarded on the basis of the proximity of any eye movement or muscle artifact to the point of decision--the positive going peak (P300) that appears during cognitive processing at about 300 msec post stimulus--that would artifactually enhance the amplitude of interest to the study. Since during this process muscle artifact and eye movement were found to be at minimum levels, the decision was made to allow the battery to automatically average the 40 individual responses without investigator intervention. The battery then separated and displayed the averaged response to the 20 positive and the 20 negative stimulus presentations, and tagged the highest amplitude peak in both tracings within a specified region (250 to 600 msec). Finally, the tracings were plotted accompanied by the amplitude and the latency of the P300. Since the critical decision in terms of the task was to identify the positive set, the P300 amplitude to the positive set should be larger than to the negative. An example of a typical output trace appears in Figure 2.

Analysis of the postvalium amplitude and latency measures of this task failed to reach significance for all memory sets, both positive and negative, except in the case of the latency of the most difficult positive memory set (memory set 5).

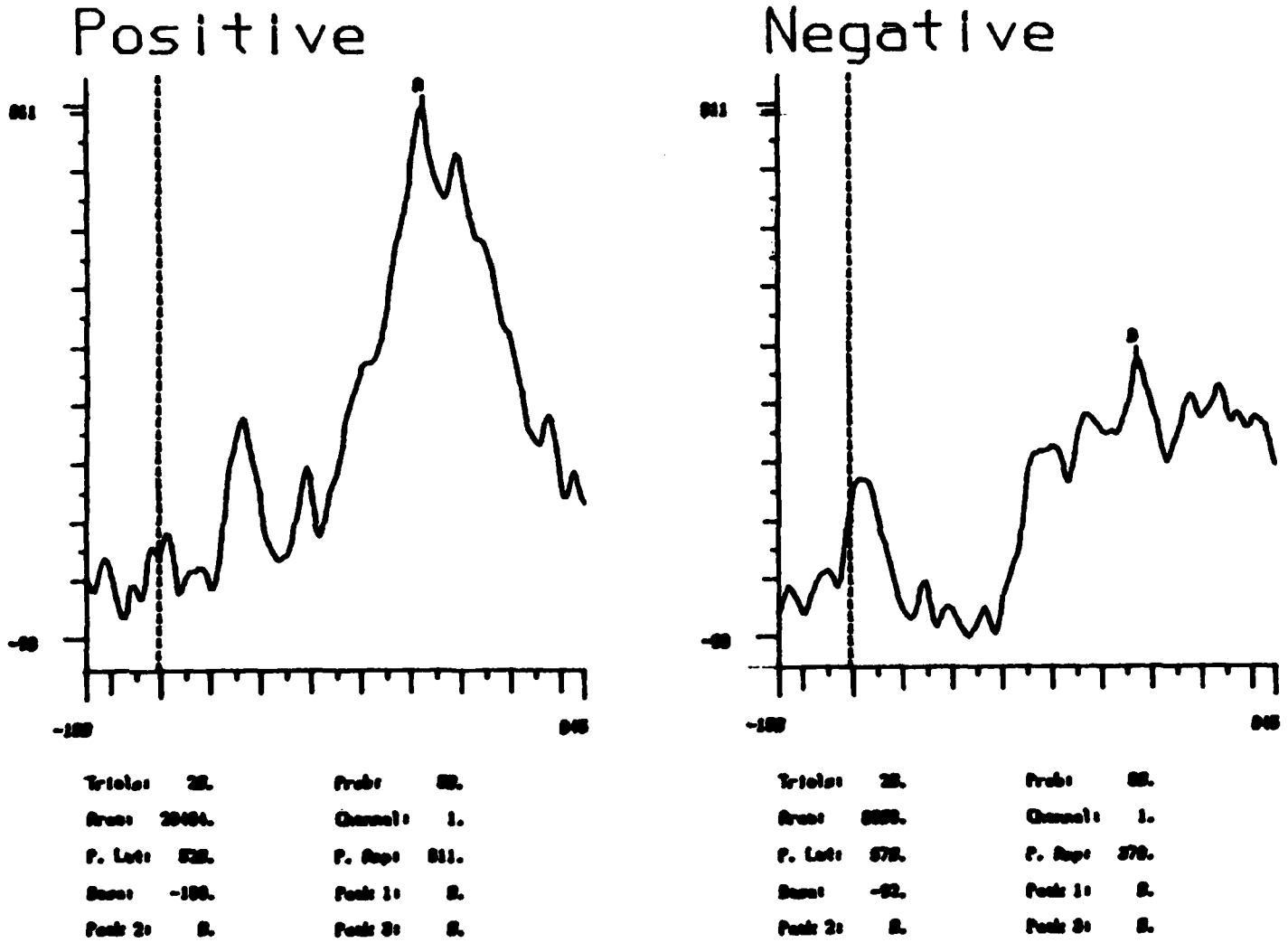

Figure 2. Typical Averaged Output for a Single Subject of P300 Response to Sternberg Task

AUDITORY TASK

The auditory oddball paradigm analysis is presented in Table 3.

TABLE 3. SESSION MEANS FOR AUDITORY ODDBALL TASK

Measure	% Correct/ Tone Set	Baseline 1	Placebo	Baseline 2	Valium	P
Percent Correct		99.29	98.29	98.71	96.63	.28
P300 Latency (msec)	Positive Tone	282.70	288.80	284.40	301.30	.39
	Negative Tone	294.20	307.30	295.00	283.50	.56
P300 Amplitude (arbitrary units)	Positive Tone	137.30	133.90	140.14	129.70	.80
	Negative Tone	69.22	68.09	68.78	69.52	.99

This analysis was carried out much like the analysis of the Sternberg task. The software provided the correct tone count on each subject's data sheet beside which the reported tone count was recorded. The tabulation of the response counts to the low tones allowed the percent of correct responses to be calculated across the measurement sessions. As in the Sternberg task, the observed postvalium decrease in this measure also failed to reach significance.

The P300 in response to the auditory decision points was also calculated by the battery in the manner described previously. The response to the critical (low) tones and the noncritical (high) tones was calculated separately and amplitude and latency measures were obtained. Although the latency of the P300 to the critical tones increased as its corresponding amplitude decreased in the valium condition, none of the differences achieved significance.

MUSCLE TASKS

Unfortunately, the electromyographic response to the grip duration/muscle fatigue task was lost for all subjects. The frequency specifications of the electromyographic amplifiers used in the battery failed to take into account the hardwired amplification system of the tape recorders used to store the

raw activity for postexperiment analysis. In effect, the EMG signal was amplified beyond the range which the recording devices were capable of storing electrical data with any precision. Consequently, the frequency response of the signal was attenuated to the point of being uninterpretable. However, the maximum voluntary contraction data (grip strength) did not depend on the recording devices and is presented in Table 4. As can be seen, this measure did not vary significantly across measurement sessions.

TABLE 4. SESSION MEANS FOR GRIP STRENGTH TASK

Measure	Component	Baseline 1	Placebo	Baseline 2	Valium	P
MVC	Meter Displacement	795.286.00	806.00	793.30	.99	

Finally, power calculations were derived for the subtests in each category in the manner described by Morrison (1976) for use in multivariate hypothesis testing. A noncentrality parameter was first calculated for each subtest. The variables used in its derivation were: (a) the number of subjects in the subtest, (b) the difference between the averaged means of the baseline and placebo measurements and the valium measurement, and (c) the square of the pooled standard deviation. SAS probability functions were then used to calculate the power of each subtest based on its noncentrality parameter, its corresponding degrees of freedom, and a fixed alpha level of 0.10. Table 5 represents the power calculations for the subtests of the visual category, Table 6 for the Sternberg memory task, and Tables 7 and 8 for the auditory and muscle categories, respectively.

The mean differences between conditions, their accompanying standard deviations, degrees of freedom, and the number of subjects' data used in the calculations for each subtest precede the power value. A negative value in the mean differences column reflects an increase in the dependent variable of interest, and a positive sign reflects a decrease. As can be seen from the charts, power was uniformly low for the obtained differences and standard deviations across all subtests. The implications of these calculations are considered below.

TABLE 5. MEAN DIFFERENCE AND POWER CALCULATIONS FOR VISUAL TASKS

Measure	Frequency/ Component	Mean Diff	SD	DF	N	Power
Checkerboard	7.5 Hz	6.1267	16.06	3,21	24	.35*
Amplitude	10 Hz	4.3633	17.19	3,21	24	.21
(arbitrary units)	15 Hz	2.7200	11.82	3,21	24	.19*
Checkerboard	7.5 Hz	-.0033	0.1835	3,21	24	.15
Latency	10 Hz	-.0067	0.4135	3,21	24	.14*
(sec)	15 Hz	-.0015	0.2331	3,21	24	.11
Strobe	(N1, P1)	-.0800	12.64	3,21	24	.10
Amplitude	(P1, N2)	-1.9700	15.71	3,21	24	.12
(arbitrary units)	(N2, P2)	1.7030	17.19	3,21	24	.11
	(P2, N3)	2.4470	13.45	3,21	24	.15
Strobe	(N1)	.0016	.01189	3,21	24	.12
Latency	(P1)	.0010	.01461	3,21	24	.11
Components	(N2)	-.0033	.01373	3,21	24	.19
(N1-N3)	(P2)	-.0062	.02244	3,21	24	.23
(sec)	(N3)	-.0048	.03199	3,21	24	.14
SS Mean	Low	.0390	.10030	3,21	24	.36*
Coherence	Medium	.0671	.13860	3,21	24	.50*
	High	-.0012	.07677	3,20	23	.10
SS Mean	Low	.0054	.04277	3,21	24	.12
Amplitude	Medium	.0002	.01147	3,21	24	.10
(arbitrary units)	High	.0010	.01285	3,20	23	.11
SS Trans	Low	52.97	116.20	3,14	17	.32
Speed	Medium	-.3667	75.97	3,17	20	---
(msec)	High	-20.53	93.41	3,5	8	---
CFF		-.240	3.623	3,21	24	.11

*Tests found significant; (-) reflects increase, (+) reflects decrease.

TABLE 6. MEAN DIFFERENCE AND POWER CALCULATIONS FOR STERNBERG SHORT TERM MEMORY TASK

Measure	M Set	Mean Diff	SD	DF	N	Power
Percent Correct	Neg M Set 1	.3933	4.945	3,14	17	.11
	Pos M Set 1	1.0833	4.559	3,14	17	.16
	Neg M Set 3	.9300	5.631	3,15	18	.13
	Pos M Set 3	2.1333	6.920	3,15	18	.21
	Neg M Set 5	2.2167	6.743	3,15	18	.23
	Pos M Set 5	4.4467	11.480	3,15	18	.28
Mean Reaction Time (msec)	Neg M Set 1	-20.6667	90.62	3,14	17	.15
	Pos M Set 1	-12.4667	86.90	3,14	17	.12
	Neg M Set 3	-.0667	98.60	3,15	18	.10
	Pos M Set 3	13.3000	109.80	3,15	18	.12
	Neg M Set 5	-49.8667	133.40	3,15	18	.26
	Pos M Set 5	-15.3333	113.40	3,15	18	.12
RT Slope	Negative Set	-8.4233	28.75	3,14	17	.19
	Postive Set	-3.0900	27.48	3,14	17	.11
P300 Amplitude (arbitrary units)	Pos M Set 1	-6.0667	55.75	3,15	18	.11
	Pos M Set 3	-1.1333	50.69	3,15	18	.10
	Pos M Set 5	-1.5000	54.58	3,15	18	.10
	Neg M Set 1	-.6667	42.64	3,15	18	.10
	Neg M Set 3	1.4400	47.64	3,15	18	.10
	Neg M Set 5	-1.4767	39.07	3,15	18	.10
P300 Latency (msec)	Pos M Set 1	-6.3667	65.81	3,15	18	.11
	Pos M Set 3	15.5330	82.09	3,15	18	.14
	Pos M Set 5	59.6300	93.82	3,15	18	.57*
	Neg M Set 1	22.8000	80.48	3,15	18	.19
	Neg M Set 3	32.9330	95.10	3,15	18	.24
	Neg M Set 5	43.8000	113.40	3,15	18	.28

*Test found significant; (-) reflects increase, (+) reflects decrease.

TABLE 7. MEAN DIFFERENCE AND POWER CALCULATIONS FOR AUDITORY ODDBALL TASK

Measure	% Correct/ Tone Set	Mean Diff	SD	DF	N	Power
Percent Correct			2.1330	3.614	3,21	24.66
P300 Latency (msec)	Positive Tone	-16.0000	37.85	3,21	24	.41
	Negative Tone	15.3330	78.71	3,21	24	.16
P300 Amplitude (arbitrary units)	Positive Tone	7.4000	42.46	3,20	23	.15
	Negative Tone	-.8233	23.99	3,20	23	.10

(-) relfects increase, (+) reflects decrease.

TABLE 8. MEAN DIFFERENCE AND POWER CALCULATIONS FOR GRIP STRENGTH TASK

Measure	Component	Mean Diff	SD	DF	N	Power
MVC	Meter Displacement	2.433	136.7	3,21	24	.10

(-) reflects increase, (+) reflects decrease.

Section 5
DISCUSSION AND CONCLUSIONS

Results showed no significant generalized effect of a 5 mg oral dose of valium on most of the dependent variables considered in this study. Given the fact that the majority of literature in this area needed 10 to 20 mg of oral valium to achieve significance in many of these variables, the result is not surprising. The few variables that were significantly affected in the present study were exclusively in the visual evoked response and memory categories, and it is with these variables that the discussion begins.

Considering the amplitude and latency changes to the pattern reversing checkerboard following valium ingestion, it is necessary to keep in mind that these measures have been used extensively in clinical medicine as indicators of various visual system pathologies (Asselman, Chadwick, and Marsden, 1975; Celesia and Daley, 1977; Halliday, Barett, Halliday, and Michael, 1977). Abnormalities in the evoked response to patterned stimuli seem not to be specific for a given disease, but rather indicate a disturbance of function somewhere in the visual pathways. The amplitude of this evoked response is decreased by any process producing changes in visual acuity or poor fixation on the stimulus screen (thus the necessity of our observation of the subjects' direction of gaze). Its latency is increased by any process decreasing synaptic transmission speed. Astigmatism, glaucoma, amblyopia, and certain forms of optic neuritis and multiple sclerosis have all been found to produce decreases in the amplitude and increased latency of the pattern evoked response (see Chiappa and Ropper, 1982, for a review). Interestingly, many of the observed changes in the evoked response precede any subjective awareness or clinically observable signs of visual system dysfunction--thus their usefulness as early indicators of progressive pathology. The frequency range of stimulation that produces the most consistent and stable results in terms of latency increases is the medium range used in this study. Amplitude changes often accompany these latency shifts but do not necessarily have to accompany them for a determination of abnormality (Starr, Sohmer, and Celesia, 1978). Since our study used valium, whose action is one of presynaptic inhibition (primarily a latency factor), the observed significant increase in the latency to the 10 Hz

stimulation is in accord with clinical findings. The amplitude changes to the 7.5 and 15 Hz stimulation may reflect some loss of acuity as well, but it is necessary in both cases to distinguish between statistical and substantive significance. The research on evoked potential abnormalities has established parameters of clinical relevance in terms of the magnitude of change required before a substantive classification of functional abnormality can be claimed. For example, in the use of the latency of evoked potentials in the diagnosis of multiple sclerosis, the change in this measure from normal controls is not considered abnormal until it approaches a difference of about 15 msec. Although in the correct direction, the overall latency increases observed in this study were only a fraction of that amount. Similarly, regarding amplitude, meaningful abnormality is not usually considered until the decrement approaches a 30 to 50 percent reduction--again, not quite what our results achieved. Thus, although the 5 mg dose of valium used in this study did affect the amplitude and latency of the checkerboard response in the hypothesized direction, the overall results do not reflect a substantive abnormality of function.

Latency increases and amplitude decreases were also observed in the evoked response to the strobe stimulus, particularly in the later components (N2, P2, and N3) in agreement with previous findings by Saletu (1974) using larger doses of valium on this measure, but none of our changes were of sufficient magnitude to achieve significance (mean change in amplitude was 1.7 to 2.4 and mean change in latency was about 5 to 6 msec).

That the visual system was being affected in our study is further reflected in the results of the steady state evoked response to unpatterned stimuli. The significant coherence decrements do reflect the fact that, in the low and medium frequency ranges, the brain's output under the influence of valium was less correlated with stimulus input--probably as a function of the amplitude decreases and phase lag increases--but since none of these changes reached significant levels, this conclusion is only speculative.

In the Sternberg memory task, the observed changes in error rate and reaction time were, again, primarily in the hypothesized direction while failing to reach significance. The percentage of correct responses

decreased slightly under the valium condition and the reaction time increased slightly. The reaction time slope also increased, indicating slight increases in memory scanning and processing time (Gomer, Spicuzza, and O'Donnell, 1976). Studies using larger doeses of valium (10 to 20 mg) report significant reductions in recall ability using both number and word series (reviewed in Kleinknecht et al., 1975). Since valium at these dosage levels reduces the ability to retrieve information, an increased latency for processing time would be a logical consequence. In the one Sternberg latency test to achieve significance, that of the P300 latency to the decision point under the heaviest memory load (memory set 5), the measure actually decreased. That this occurred even though the mean reaction time to this same memory set increased (although nonsignificantly) is probably reflective of a quicker, more confident (though inaccurate) cognitive decision point due, perhaps, to a valium mediated decrease in anxiety. However, since the latency of the P300 normally varies from 250 to 500+ msec, this result can also be explained by random fluctuation.

Similarly, the results of the auditory P300 can also be ascribed to such a random fluctuation occurring within normal parameters.

Finally, the fact that grip strength did not fluctuate across conditions supports the conclusion that the 5 mg dose had no significant gross muscular effect in terms of the strength of the dominant forearm. The ability to maintain that strength over time could have been obtained by the fatigue rate measure as a function of the electromyographic frequency decrease had it not been lost due to equipment malfunction.

In summary, these results indicate that an orally administered 5 mg dose of valium produces little significant effect on the variables measured in this study. The power calculations presented in Table 5 to Table 8 are generally low--reflecting a low probability of being able to find a significant difference where one actually exists. However, the literature indicates that differences of the magnitude obtained in the present study are without substantive meaning in terms of decrements in performance capabilities. The power of these tests could be increased by measuring greater numbers of subjects at this dosage level. The intersubject variability in the response to

the 5 mg dose would be reduced in this manner and the chance of achieving significance would increase-perhaps resulting in greater statistical significance of the observed valium induced changes at this dosage level. However, the statistical result would have little substantive meaning in the real world in terms of performance capabilities. Based on these considerations, it would seem to make more sense to attempt to increase the effect size (and hence the power) in line with the majority of the literature in this area--by increasing the dosage level to 10, 15, or 20 mg in a treatment-by-levels approach. The statistical significance found with increased power in this manner would have substantive meaning. Approval of a 10 mg dose has already been approved by the Human Use Review Committee of the Armstrong Aerospace Medical Research Laboratory and design planning is underway.

Finally, the averaging and analysis capabilities of the battery used in this study were thoroughly tested and, in general, exceeded expectations. Further refinements are already being undertaken in terms of its electromyographic frequency analysis difficulties, and the software errors that caused the data loss in the Sternberg task have already been corrected. The battery has generally demonstrated capabilities worthy of its employment in future studies and will be ready within the next 4 to 8 weeks for its next test.

REFERENCES

Asselman, P., Chadwick, D. W., and Marsden, C. D., 1975, Visual Evoked Responses in the Diagnosis and Management of Patients Suspected of Multiple Sclerosis, Brain, 98, 261-282.

Beck, E. C., 1975, Electrophysiology and Behavior. In Annual Review of Psychology (M. R. Rosenzweig and L. W. Porter, Eds.), 233-262.

Celesia, G. G. and Daly, R. F., 1977, VECA: A New Electrophysiological Test for the Diagnosis of Optic Nerve Lesions, Neurology (Minn.), 27, 637-641.

Chapman, R. M., 1965, Evoked Responses to Relevant and Irrelevant Visual Stimuli While Problem Solving, Proceedings of the 73rd Annual Convention of the American Psychological Association, 177-178.

Chapman, R. M., 1973, Evoked Potentials of the Brain Related to Thinking. In The Psychophysiology of Thinking (F. J. McGugian and R. A. Schoonover, Eds.), Academic Press: New York.

Chiappa, K. H. and Ropper, A. H., 1982, Evoked Potentials in Clinical Medicine, The New England Journal of Medicine, 306, 1140-1150.

Clarke, P. R. F., Eccersely, P. S., Frisby, J. P., and Thornton, J. A., 1970, Amnesiac Effects of Diazepam, British Journal of Anaesthesiology, 42, 690-697.

Davies, D. R. and Parasuramen, R., 1977, Cortical Evoked Potentials and Vigilance: A Decision Theory Analysis. In Vigilance: Theory, Operational Performance, and Physiological Correlates (R. R. Mackie, Ed.), New York: Plenum Press.

Davis, H., 1964, Enhancement of Cortical Evoked Potentials in Humans Related to a Task Requiring a Decision, Science, 145, 182-183.

Davis, H., 1976, Principles of Electric Response Audiometry, St. Louis: Beltone Institute for Hearing Research.

Donchin, E., 1968, Average Evoked Potentials and Uncertainty Resolution, Psychonomic Science, 12, 103.

Donchin, E., 1975, Brain Electric Correlates of Pattern Recognition. In Signal Analyses and Pattern Recognition in Biomedical Engineering (G. F. Inbar, Ed.), New York: Wiley.

Donchin, E., 1977, Determinations and Identifications of Human Brain Wave Patterns Associated with Cognitive and Performance Effects in Operational Settings, Progress Reports Abstracts, Physiology Program, Office of Naval Research.

Donchin, E. and Cohen, L., 1967, Averaged Evoked Potentials and Intramodality Selective Attention, Electroencephalography and Clinical Neurophysiology, 22, 537-546.

Donchin, E. and Cohen, L., 1969, Anticipation of Relevant Stimuli and Evoked Potentials: A Reply to Naatanen, Perceptual and Motor Skills, 29, 115-117.

Donchin, E., Kubovy, M., Kutas, M., Johnson, R., and Herning, R., 1973, Graded Changes in Evoked Response (P300) Amplitude as a Function of Cognitive Activity, Perception and Psychophysics, 14, 319-324.

Donchin, E. and Lindsley, D. B., 1966, Cortical Evoked Potentials and Reaction Times, Electroencephalography and Clinical Neurophysiology, 20, 217-223.

Donchin, E. and Sutton, S., 1970, The Psychological Significance of Evoked Responses: A Comment on Clark, Butler, and Rosner, Communications in Behavioral Biology, 5, 111-114.

Gomer, F. E., Spicuzza, R. J., and O'Donnell, R. D., 1976, Evoked Potential Correlates of Visual Item Recognition During Memory Scanning Tasks, Physiological Psychology, 4, 61-65.

Haffner, J. F., Morland, J., Stekleiv, J., Stromsaether, C. E., Danielsen, A., Frivik, P. T., and Dybing, F., 1973, Mental and Psychomotor Effects of Diazepam and Alcohol, Acta. Pharmacol. Toxicol, 32, 161-178.

Halliday, A. M., Barrett, G., Halliday, E., and Michael, W. F., 1977, The Topography of the Pattern Evoked Potential. In Visual Evoked Potentials in Man: New Developments (J. E. Desmedt, Ed.), Oxford University Press, 121-133.

Hecox, K. and Galambos, R., 1974, Brainstem Auditory Evoked Responses in Human Infants and Adults, Otolaryingology, 99,30-33.

Jasper, H. H., 1958, Report of Vommittee on Methods of Clinical Examination in EEG: Appendix: The Ten-Twenty Electrode System of The International Federation, Electroencephalography and Clinical Neurophysiology, 10, 371-375.

Jewett, D. and Williston, J., 1971, Auditory Evoked Far Field Averages from the Scalp of Human, Brain, 94, 681-696.

Kleinknecht, R. A. and Donaldson, D., 1975, A Review of the Effects of Diazepam on Cognitive and Psychomotor Performance, Journal of Nervous and Mental Disease, 161, 399-411.

Kutas, M., McCarthy, G., and Donchin, E., 1977, Augmenting Mental Chronometry: The P300 as a Measure of Stimulus Evaluation Time, Science, 197, 792-795.

Liljequist, R., Linnoila, M., and Mattila, M. J., 1978, Effect of Diazepam and Chlorpromazine on Memory Functions in Man, European Journal of Clinical Pharmacology, 13, 339-342.

Longo, V. G., 1972, Neuropharmacology and Behavior, W. H. Freeman and Co., 88-89.

Marg, E., Freeman, D. N., Peltzman, P., and Goldstein, P. J., 1976, Visual Acuity Development in Human Infants: Evoked Potential Measurements, Investigative Opthalmology, 15, 150-153.

Morrison, J. F., 1976, Multivariate Statistical Methods, McGraw-Hill: New York, 160-161.

Physician's Desk Reference, 1979, 1466-1468.

Regan, D., 1973, Rapid Objective Refraction Using Evoked Brain Potentials, Investigative Opthalmology, 15, 669-679.

Regan, D., 1975, Color Coding of Pattern Responses in Man Investigated by Evoked Potential Feedback and Direct Plot Techniques, Vision Research, 15, 175-183.

Regan, D., 1977a, Steady State Evoked Potentials, Journal of the Optical Society of America, 67, 1475-1488.

Regan, D., 1977b, Speedy Assessment of Visual Acuity in Amblyopia by Evoked Potential Method, Opthalmologica, 175, 159-164.

Rizzuto, A. P., and O'Donnell, R. D., 1981, Visually Evoked Brain Potentials and Operator Workload, Association of Graduates Quarterly, Air Force Institute of Technology, 2, 4-5.

Seppala, T., Pavla, E., Mattila, M. J., Kortilla, K., and Shrotriya, R. C., 1980, Tofisopam, a Novel 3,4-Benzodiazepine: Multiple Dose Effects on Psychomotor Skills and Memory. Comparison with Diazepam and Interactions with Ethanol, Psycho Pharmacology, 64, 209-218.

Shafer, E. W. P., 1977, Brain Response to Television Reflects Interest, Psychophysiology, 14, 115.

Shagass, C., 1974, Effects of Psychotropic Drugs on Human Evoked Potentials, Modern Problems in Pharmacopsychiatry, 8, 238-257.

Shagass, C. and Straumanis, J. J., 1978, Drugs and Human Sensory Evoked Potentials, In Psychopharmacology: A Generation of Progress (M. A. Lipton, Ed.), New York: Raven Press.

Sherwin, I., 1971, Differential Action of Diazepam on Evoked Cerebral Responses, Electroencephelography and Clinical Neurophysiology, 30, 445-452.

Squires, K. C., Wickens, C., Squires, N. K., and Donchin, E., 1976, The Effect of Stimulus Sequence on the Waveform of the Cortical Event-Related Potential, Science, 193, 1142-1146.

Starr, A., Sohmer, H., Celesia, G. G., 1978, Some Applications of Evoked Potentials to Patients with Neurological and Sensory Impairment. In Event Related Brain Potentials in Man, Academic Press, 155-211.

Sternberg, S., 1969, Memory Scanning: Mental Processes Revealed by Reaction Time Experiments, American Scientist, 57, 421-457.

Weider, A., Wolff, H. G., Brodman, K., Mittelmann, B., and Wechsler, D., 1949, The Cornell Medical Index, New York: The Psychological Corporation.

Wickens, C., Israel, J., and Donchin, E., 1977, The Event Related Cortical Potential as an Index of Task Workload, Proceedings of the Human Factors Society, 21st Annual Meeting, San Francisco.

Wilson, G. F. and O'Donnell, R. D., 1980, Human Sensitivity to High Frequency Sine Wave and Pulsed Light Stimulation as Measured by the Steady State Cortical Evoked Response, Technical Report, Air Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio.

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